L64 ANSWER 8 OF 21 MEDLINE DUPLICATE 3

ACCESSION NUMBER: 1999344054 MEDLINE
DOCUMENT NUMBER: 99344054 PubMed ID: 10415565
TITLE: Review--the use of immunosuppressive agents to prevent neutralizing antibodies against a transgene product.
AUTHOR: Potter M A; Chang P L
CORPORATE SOURCE: Department of Medical Biochemistry, McMaster University, Hamilton, Ontario, Canada.
SOURCE: ANNALS OF THE NEW YORK ACADEMY OF SCIENCES, **(1999 Jun 18)** 875 159-74. Ref: 26
Journal code: 7506858. ISSN: 0077-8923.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 19990816
Last Updated on STN: 19990816
Entered Medline: 19990805

AB A potential obstacle to successful gene therapy for some patients is the in vivo production of neutralizing antibodies against the recombinant therapeutic product delivered. This is a problem inherent to all gene therapy methods, regardless of the vector used to deliver the protein. This clinical situation can be mimicked in animal models by delivering a foreign protein (i.e., a human protein) to the animal to provoke anti-human protein antibody production. The efficacy of different immunosuppressive treatments to inhibit the development of neutralizing antibodies can then be investigated. The immunosuppressive agents examined here include drugs (e.g., cyclophosphamide, **FK506**), cytokines (e.g., interferon-gamma, interleukin-12), and monoclonal antibodies (e.g., anti-CD4, anti-gp39, **CTLA4**-Ig). It has been found that a high level of antibody suppression is necessary to allow prolonged delivery of a foreign protein. Immunosuppressive agents capable of this high level of suppression will be important adjuncts to prevent treatment failures in situations where patients are at risk of developing neutralizing antibodies.

L64 ANSWER 9 OF 21 CAPLUS

not ordered

L64 ANSWER 14 OF 21 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1999:19227 BIOSIS

DOCUMENT NUMBER: PREV199900019227

TITLE: **Rapamycin** but not cyclosporine preserves the beneficial effects of costimulation blockade.

AUTHOR(S): Li, Yongsheng; Zheng, Xin Xiao; Li, Xan Chang; Zand, Martin S.; Strom, Terry B.

CORPORATE SOURCE: Harv. Med. Sch., Beth Isr. Deaconess Med. Cent., Boston, MA USA

SOURCE: Journal of the American Society of Nephrology, (**Sept., 1998**) Vol. 9, No. PROGRAM AND ABSTR. ISSUE, pp. 654A. Meeting Info.: 31st Annual Meeting of the American Society of Nephrology Philadelphia, Pennsylvania, USA October 25-28, 1998 American Society of Nephrology . ISSN: 1046-6673.

DOCUMENT TYPE: Conference

LANGUAGE: English

L64 ANSWER 13 OF 21 MEDLINE DUPLICATE 5

ACCESSION NUMBER: 1998312632 MEDLINE
DOCUMENT NUMBER: 98312632 PubMed ID: 9650612
TITLE: Suppression of immunological response against a transgene product delivered from microencapsulated cells.
AUTHOR: Potter M A; Hymus S; Stockley T; Chang P L
CORPORATE SOURCE: Department of Medical Biochemistry, McMaster University, Hamilton, Ontario, Canada.
SOURCE: HUMAN GENE THERAPY, **(1998 Jun 10)** 9 (9) 1275-82. Journal code: 9008950. ISSN: 1043-0342.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 19980925
Last Updated on STN: 19980925
Entered Medline: 19980916

AB A potential obstacle to successful gene therapy for some patients is the in vivo production of neutralizing antibodies against the recombinant therapeutic product delivered. To mimic this clinical situation, we implanted microencapsulated recombinant cells producing human growth hormone into C57B1/6 mice to provoke antihuman growth hormone antibody production. We then investigated the efficacy of different immunosuppressive treatments to inhibit the development of neutralizing antibodies. The experimental mice were treated with either an immunosuppressive drug (**FK506** or cyclophosphamide), a cytokine (interferon-gamma [IFN-gamma] or interleukin-12 [IL-12], or a monoclonal antibody (anti-CD4, anti-gp39, or **CTLA4**-Ig). Serum human growth hormone and mouse anti-human growth hormone antibody levels were measured by enzyme-linked immunosorbent assay (ELISA) for 4 weeks. There were three patterns of response noted among the seven treatment groups. First, the mice receiving IFN-gamma, IL-12, anti-gp39, or **CTLA4**-Ig were similar to the untreated controls-no suppression of anti-hGH antibodies and no improvement in delivery of hGH. Next, the mice receiving **FK506** or cyclosphosphamide showed > or = 90% suppression of antibodies but also no improvement in product delivery. Last, the mice receiving anti-CD4 showed almost complete antibody suppression over 1 month postimplantation. Furthermore, only anti-CD4 permitted a sustained level of human growth hormone delivery to day 28, in contrast to the controls whose human growth hormone delivery was undetectable by day 14 postimplantation. Hence, the use of anti-CD4 inhibited formation of neutralizing antibodies against a recombinant gene product delivered in vivo, and allowed prolonged delivery of a foreign protein. Its role as adjunct treatment for appropriate patients receiving gene therapy should be examined further.

L60 ANSWER 1 OF 14 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 1999207078 MEDLINE
DOCUMENT NUMBER: 99207078 PubMed ID: 10190907
TITLE: Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) can regulate **dendritic** cell-induced activation and cytotoxicity of CD8(+) T cells independently of **CD4**(+) T cell **help**.
AUTHOR: McCoy K D; Hermans I F; Fraser J H; Le Gros G; Ronchese F
CORPORATE SOURCE: Malaghan Institute of Medical Research, Wellington School of Medicine, Wellington, New Zealand.
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, **(1999 Apr 5)** 189 (7) 1157-62.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 19990517
Last Updated on STN: 19990517
Entered Medline: 19990506

AB The mechanisms that regulate the strength and duration of CD8(+) cytotoxic T cell activity determine the effectiveness of an antitumor immune response. To better understand the antitumor effects of anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) antibody treatment, we analyzed the effect of CTLA-4 signaling on CD8(+) T cells in vitro and in vivo. In vitro, cross-linking of CTLA-4 on purified CD8(+) T cells caused decreased proliferative responses to anti-**CD3** stimulation and rapid loss of activation marker expression. In vivo, blockade of CTLA-4 by neutralizing anti-CTLA-4 mAb greatly enhanced the accumulation, activation, and cytotoxic activity of CD8(+) T cells induced by immunization with Ag on **dendritic** cells (DC). This enhanced response did not require the expression of MHC class II molecules on DC or the presence of CD4(+) T cells. These results demonstrate that CTLA-4 blockade is able to directly enhance the proliferation and activation of specific CD8(+) T cells, indicating its potential for tumor immunotherapy even in situations in which **CD4**(+) T cell **help** is limited or absent.

L64 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:113814 CAPLUS
DOCUMENT NUMBER: 130:163982
TITLE: Method enabling readministration of adeno-assocd. virus vector to human patients via immunosuppression
INVENTOR(S): Dwarki, Varavani; Zhou, Shang-Zhen; Murphy, John E.; Manning, William C.; Escobedo, Jaime
PATENT ASSIGNEE(S): Chiron Corporation, USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9906562	A1	19990211	WO 1998-US15794	19980729 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9886721	A1	19990222	AU 1998-86721	19980729 <--
EP 1002078	A1	20000524	EP 1998-938125	19980729
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001512142	T2	20010821	JP 2000-505303	19980729

PRIORITY APPLN. INFO.:

US 1997-54318P	P	19970731
US 1997-54372P	P	19970731
US 1997-54689P	P	19970731
US 1997-54692P	P	19970731
US 1997-56139P	P	19970819
WO 1998-US15794	W	19980729

AB The present invention is directed to a method for providing adeno-assocd. virus (AAV) mediated gene therapy to a patient, comprising administering to a patient a replication-defective adeno-assocd. virus particle which infects a cell in the patient, the particle having therein a gene encoding a protein needed by the patient, the gene being operatively linked for expression in the cell, and at about the time of above-administering step, also administering to the patient an immunosuppressant that suppresses the patient's humoral immune response. This allows for expression of a gene encoded by the AAV vector without inducing a neutralizing immunoresponse. The present invention is also directed to pharmaceutical compns. comprising the above described adeno-assocd. virus and humoral immuno-suppressant in a pharmaceutically acceptable carrier. Examples of proteins expressed by the above-described vectors include erythropoietin, thrombopoietin, human growth factor, leptin, Factor VIII, Factor IX, Factor Xa and the like.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

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